D4

26. (Amended) The method of claim 25 in which the enzyme has a purity, in U/μg of purified protein, of at least 95%.

REMARKS

Claims 9-23, 25 and 26 were pending in the application. Claims 9, 14, 20, 25, and 26 have been amended. Upon entry of these amendments, Claims 9-23, 25, and 26 will be pending and under active consideration. Claims 9 and 20 are independent. A marked-up version of the claims indicating the changes to the claims is attached hereto as Exhibit A. A copy of all pending claims, as amended, is attached hereto as Exhibit B. The amendments are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter.

Claims 9 and 20 are amended to add the phrase "wherein at least 70% of said sucrose is converted to α-1,4-glucans and fructose within 23.5 hours." The amendments are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter. In particular, support for the amendments is found in Figure 1 of the specification as filed.

Claims 14, 25, and 26 are amended to add the phrase "in U/μg of purified protein" after the term "purity." The amendments are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter. In particular, support for the amendments is found at lines 5-8 on page 15 of the specification as filed.

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Final Office Action are respectfully requested.

I. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

A. The Rejection Over Published Patent Application WO 95/31553 To Kossman *et al.*

The Final Office Action, at pages 3-6, rejects Claims 9-15 and 20-26 as allegedly being obvious over Published Patent Application WO 95/31553 to Kossman *et al.* (hereinafter, "Kossman"), under 35 U.S.C. § 103(a). The Office Action alleges that Kossman discloses a process of preparing insoluble polysaccharides by contacting sucrose with an amylosucrase under aqueous conditions, that the enzyme should be obtained from the claimed microorganism, *Neisseria polysaccharea*, can be produced recombinantly, can be used in purified form, and can be used in immobilized form. While the Final Office Action acknowledges that Kossman differs from the cited claims in that Kossman does not employ the enzyme under buffer-free conditions, the Final Office Action alleges further that Kossman clearly discloses that the enzyme is useful at neutral conditions, for example at pH 6.5. Thus, the Final Office Action alleges that the artisan of ordinary skill, recognizing from Kossman that the enzyme is active at neutral conditions *which do not require the addition of a buffer*, clearly would have been motivated to have omitted the step of adding a buffer to the reaction medium disclosed by Kossman in order to make the process easier and cheaper by omitting the expense of a buffer. The Final Office Action alleges further still, that the artisan of ordinary skill clearly had a reasonable expectation that the process would work in the absence of a buffer, based on the fact that the Kossman discloses the enzyme as functioning at neutral conditions. Applicants traverse respectfully.

Applicants submit respectfully that Claims 9-15 and 20-26, as amended, are not rendered obvious by Kossman. Examiner asserts in the Response to Argument, at page 7 of the Final Office Action, that "applicant's claims do not require a specific yield or duration for the reaction. Thus, even if the artisan of ordinary skill expected a buffer-free reaction to work less efficiently that a buffered reaction, the artisan of ordinary skill viewing Kossman still would have had a reasonable expectation that the buffer-free reaction medium would have produced the α-glucans as recited in the claims." Applicants submit respectfully that independent Claims 9 and 20, from which Claims 10-14 and 21-26 depend, are amended herein to provide specific yield and duration for the reaction. In light of Applicants' arguments (made in Applicants' previous Amendment and Response of May 13, 2002, and reiterated below for Examiner's convenience) that one skilled in the art would indeed expect a buffer-free reaction to work inefficiently, or not at all, Applicants submit respectfully that the rejection of Claims 9-15 and 20-26 under 35 U.S.C. § 103(a) has been overcome.

While the Office Action is correct in asserting that Kossman clearly discloses that the enzyme having amylosucrase activity is useful at neutral conditions, for example at page 35 wherein the enzyme is employed at pH 6.5, Applicants submit respectfully that the Office Action is in error when it draws from this teaching the inference that one skilled in the art would expect that maintenance of neutral conditions in a reaction solution does not require the addition of a buffer. Applicants submit respectfully that the skilled artisan would recognize that, while purified water indeed has a neutral pH, once reaction components are added to purified water, the pH of the aqueous solution changes. Applicants submit respectfully that the skilled artisan would recognize that a buffer is used, specifically and intentionally, to ***create and maintain*** given pH conditions in a reaction solution-- neutral conditions in this case-- that would otherwise

not exist or remain at the given pH owing to the constituents and products of the given chemical reaction occurring in the solution. Applicants submit respectfully that one skilled in the art would be expected, further, to recognize that the presence of an ongoing chemical reaction in the aqueous solution would tend to drive the pH of the solution even further away from neutral conditions.

Applicants submit respectfully that one skilled in the art would recognize that, in enzymatic reactions, reaction efficiency is degraded substantially, or decreases to zero, when the reaction conditions vary from the optimum conditions recommended for the reaction. In order to maintain the recommended optimum reaction conditions, for example to prevent harmful variations in pH, the skilled artisan routinely employs a suitable buffer. Applicants respectfully draw Examiner's attention to Claims 9 and 20, as amended, which now recite "wherein at least 70% of said sucrose is converted to α-1,4-glucans and fructose within 23.5 hours." Applicants submit respectfully that one skilled in the art would not reasonably expect a buffer-free reaction to proceed to 70% completion within 23.5 hours, as claimed.

In the Response to Argument, at page 6-7 of the Final Office Action, the examiner asserts that "there is nothing in the reference suggesting that conducting the reaction in the absence of a buffer would result in an undesirable pH shift." Applicants submit respectfully that this assertion is improper because, for a finding of obviousness, a reference must teach or suggest positively that a modification from the taught method will work. As the examiner no doubt well knows, a teaching or suggestion that a modification will not work is known as teaching away. Applicants submit respectfully that failure in a reference to teach away from a modification does not render that modification obvious over the reference.

"To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Applicants submit respectfully that Kossman does not expressly or impliedly suggest the claimed invention, and Applicants further submit respectfully that the examiner has not presented a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. Inasmuch as the present 35 U.S.C. § 103(a) rejection of Claims 9-15 and 20-26 is based solely on Examiner's unsupported assertion that one skilled in the art would have been motivated to exclude from his reaction the buffer disclose in Kossman, despite the fact that Kossman makes no teaching or suggestion that the reaction would be expected to succeed in the absence of buffer, Applicants request respectfully that Examiner provide citation or reference in support of Examiner's assertion so that Applicants will have free and fair opportunity to rebut Examiner's argument, as required under MPEP 2144.03.

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Applicants submit respectfully that, in light of the well-known propriety in using buffers to maintain appropriate reaction conditions for enzymatic reactions, and the equally well-known costs for failure to maintain reaction conditions in enzymatic reactions (*i.e.*, loss of reaction efficiency and/or risk of complete reaction failure), one

skilled in the art would ***not*** be motivated to attempt the reactions disclosed in Kossman in the absence of the suggested buffer.

Accordingly, Applicant requests respectfully that the 35 U.S.C. § 103(a) rejection of Claims 9-15 and 20-26 be withdrawn.

B. The Rejection Over Kossman In View Of Remaud-Simeon

At page 5-6, the Final Office Action rejects Claims 9-26 under 35 U.S.C. § 103(a) as being unpatentable over Kossman in view of Remaud-Simeon (Carbohydrate Bioengineering 1995:313-320). While acknowledging that Kossman differs from Applicants' claimed invention in that Kossman does not disclose the addition of a polysaccharide acceptor which may be dextrin, glycogen or amylopectin, the Final Office Action alleges that Remaud-Simeon cures the deficiencies of Kossman by disclosing that glycogen, starch (which contains amylopectin) and maltooligosaccharides act to activate amylosucrase when they are added to the reaction medium. The Final Office Action alleges that, thus, the artisan of ordinary skill would have been motivated to have added glycogen and amylopectin to the reaction medium to have afforded the activating effect disclosed by Remaud-Simeon. Moreover, the Final Office Action alleges that, in view of the fact that dextrins are very similar chemically to the compounds disclosed by Remaud-Simeon as having an activating effect on amylosucrase, the artisan of ordinary skill would have had a reasonable expectation that dextrins would have had the same activating effect on amylosucrase as glycogen, starch (which contains amylopectin) and maltooligosaccharides, and so the Final Office Action alleges that the artisan of ordinary skill would, therefore, have been motivated to have added dextrin to the reaction medium used for the production of glucans by amylosucrase. Applicants traverse respectfully.

Applicants submit respectfully that Kossman, either alone or in view of Remaud-Simeon, does not render Claims 9-26 obvious under 35 U.S.C. § 103(a). Referring to Applicants' arguments made above in support of Claims 9-15 and 20-26, Applicants submit respectfully that Kossman is deficient with regard to the claims of the present invention, as amended, in that Kossman fails to teach or suggest that 70% of sucrose in a buffer-free reaction mixture with amylosucrase would be converted to α-1,4-glucans and fructose within 23.5 hours. Inasmuch as the secondary reference Remaud-Simeon is not alleged to cure this deficiency in Kossman, Applicants submit respectfully that a *prima facie* case for obviousness under 35 U.S.C. § 103(a) has not been established. Accordingly, Applicants request respectfully that the rejections of Claims 9-26 under 35 U.S.C. § 103(a) be withdrawn.

II. Rejections Under 35 U.S.C. § 112, Second Paragraph

At pages 2-3 of the Final Office Action, Claims 14, 25, and 26 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out particularly and claim distinctly the subject matter regarded as the invention. The Final Office Action alleges that the recitations "a purity of at least 80%," "a purity of at least 90%," and "a purity of at least 95%," in claim 14 as amended and new claims 25 and 26, are indefinite because it is not clear whether the recitation requires a weight percentage, a molar percentage, or a percentage of a particular specific activity. Applicants traverse respectfully.

Respectfully, Applicants direct Examiner's attention to page 7, lines 8-13, and Examples 1-3, on page 13-17 of the specification as filed, and in particular to Example 1, which teaches a method of purifying an amylosucrase enzyme of the present invention, and Example 2, which

teaches the determination of the enzyme's specific activity. Page 7, lines 8-13, define the term "purified amylosucrase" as an amylosucrase that is substantially free from the cell constituents of the cells in which the protein is synthesized. A number of purification techniques are listed on page 10, lines 10-12, such as precipitation, affinity chromatography, ion exchange chromatography, gel filtration, reverse-phase HPLC, etc. Applicants submit respectfully that one skilled in the art will recognize immediately that these techniques are effective to separate a protein of interest from cellular debris, DNA, lipids, and other unwanted proteins. Likewise, Applicants submit respectfully that the protocol of Example 1 will be familiar to one skilled in the art as a method of purifying a protein of interest from a raw cell extract.

Example 2, particularly lines 5-8 on page 15 of the specification as filed, teaches that protein purity is assessed in terms of the desired enzymatic activity; in this case, amylosucrase activity. As recited in lines 6-7 on page 15, a preferred measure of purity is U/μg (units of activity per microgram of purified protein). Applicants submit respectfully that one skilled in the art will understand that impurities in the protein product will reduce the ratio of the desired enzymatic activity relative to the total amount of protein product isolated. Thus, Applicants submit respectfully that one skilled in the art will be able to determine readily the purity of amylosucrase, expressed as a percentage of the specific activity of pure amylosucrase, by comparing the known value of the specific activity of pure amylosucrase with the activity per microgram of protein product used in the methods of the present invention as claimed.

Notwithstanding the above, and without acquiescing in the propriety of the rejection under 35 U.S.C. § 112, second paragraph, Claims 14, 25, and 26 are amended herein to recite "in U/μg of purified protein," thus clarifying the measurement of the enzyme purity recited in the afore-mentioned claims.

On this basis, Applicants suggest respectfully that the rejection has been traversed, and Applicants request respectfully that the 35 U.S.C. § 112, second paragraph rejection of Claims 14, 25, and 26 be withdrawn.

CONCLUSION

Applicants submit that the application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Final Office Action, and an early Notice of Allowance are requested.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

AUTHORIZATION

Applicants believe there is no additional fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,

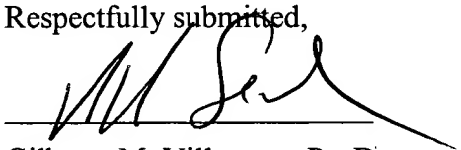

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EXHIBIT A

MARKED-UP VERSION OF THE CLAIMS
U.S. PATENT APPLICATION NO. 09/740,824

9. (Amended) A method of preparing water-insoluble α-1,4-glucans comprising contacting a reaction mixture comprising sucrose with an enzyme having amylosucrase enzymatic activity under aqueous, buffer-free conditions to provide a product mixture comprising water-insoluble α-1,4-glucans and fructose, wherein at least 70% of said sucrose is converted to α-1,4-glucans and fructose within 23.5 hours.

14. (Amended) The method of claim 9 in which the enzyme having amylosucrase enzymatic activity has a purity, in U/μg of purified protein, of at least 80%.

20. (Amended) A method of preparing water-insoluble α-1,4-glucans comprising contacting sucrose with an amylosucrase under aqueous, buffer-free conditions to provide water-insoluble α-1,4-glucans and fructose, wherein at least 70% of said sucrose is converted to α-1,4-glucans and fructose within 23.5 hours.

25. (Amended) The method of claim 9 in which the enzyme has a purity, in U/μg of purified protein, of at least 90%.

26. (Amended) The method of claim 9 in which the enzyme has a purity, in U/μg of purified protein, of at least 95%.